

TURCHETTA et al
Appl. No. 10/580,173
January 26, 2009

AMENDMENTS TO THE TITLE:

Please replace the title with the following new title:

POLYMORPHS OF 1-CYCLOPROPYL-7-(S,S)-2,8-DIAZABICYCLO[4.3.0]NON-
8-YL)-6-FLUORO-1,4-DIHYDRO-8-METHOXY-4-OXO-3-QUINOLINE CARBOXYLIC
ACID HYDROCHLORIDE AND METHODS FOR THE PREPARATION THEREOF

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AMENDMENTS TO THE SPECIFICATION:

Please amend [0001] of the specification as follows:

[0001] The present invention relates to two novel polymorphs of 4-cyclopropyl-7-([S,S])-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline-carboxylic acid hydrochloride 1-cyclopropyl-7-(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid hydrochloride, the methods for the preparation thereof, and pharmaceutical formulations which include them.

Please amend [0002] of the specification as follows:

[0002] ~~4-cyclopropyl-7-([S,S])-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline-carboxylic acid hydrochloride~~ 1-cyclopropyl-7-(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid hydrochloride, also known by the name moxifloxacin hydrochloride, is an antibacterial agent of formula: which is widely used therapeutically in the treatment of infections by antibiotic-resistant bacteria.

Please amend [0012] of the specification as follows:

[0012] d) isolating the product which is separated,

a novel hydrated crystalline form of moxifloxacin hydrochloride, which is stable and easy to formulate, designated as moxifloxacin hydrochloride form A is obtained.

Please amend [0043] of the specification as follows:

TURCHETTA et al
Appl. No. 10/580,173
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[0043] 907.4 g of moxifloxacin hydrochloride monohydrate and 9070 ml of absolute ethanol (K.F. <0.1%) were loaded into a 10 liter jacketed reactor and equipped with a mechanical stirrer, reflux condenser, and thermometer. The suspension was brought to reflux with stirring and was kept in those conditions for 4 hours. The temperature was then reduced to 20° C and the solid was filtered out and washed with 900 ml of absolute ethanol. The filtered solid was then discharged and dried under vacuum (30 mmHg) at 40° C for 18 hours to give moxifloxacin hydrochloride form A having a water content of about 1% (K.F.).

Please amend [0044] of the specification as follows:

[0044] 10 g of anhydrous moxifloxacin hydrochloride and 200 ml of ethanol with 0.3% K.F. were loaded into a 250 ml flask. The mixture was brought to reflux and kept in those conditions for 4 hours, after which it was cooled to room temperature. The solid product was filtered out and washed with 30 ml of absolute ethanol. The solid was dried under vacuum (30 mmHg) at 40° C for 16 hours to give 8.5 g of moxifloxacin hydrochloride form A.

Please amend [0045] of the specification as follows:

[0045] 20 g of anhydrous moxifloxacin hydrochloride and 250 ml of isopropanol with 0.2% K.F. were loaded into a 500 ml flask. The mixture was brought to reflux and was kept in those conditions for 4 hours, after which it was cooled to room temperature. The solid product was filtered out and washed with 50 ml of isopropanol. The solid was dried under vacuum (30 mmHg) at 40° C for 16 hours, to give 8.0 g of moxifloxacin hydrochloride form A.

TURCHETTA et al
Appl. No. 10/580,173
January 26, 2009

Please amend [0046] of the specification as follows:

[0046] 10 g of anhydrous moxifloxacin hydrochloride and 200 ml of isobutanol with 0.3% K.F. were loaded into a 250 ml flask. The mixture was brought to reflux and was kept in those conditions for 4 hours, after which it was cooled to room temperature. The solid product was filtered out and washed with 30 ml of absolute ethanol. The solid was dried under vacuum (30 mmHg) at 40° C for 16 hours to give 7.8 g of moxifloxacin hydrochloride form A.

Please amend [0047] of the specification as follows:

[0047] 10 g of moxifloxacin hydrochloride monohydrate and 200 ml of 1,2-propandiol with 0.1% K.F. were loaded into a 250 ml flask. The mixture was brought to reflux and was kept in those conditions for 4 hours, after which it was cooled to room temperature. The solid product was filtered out and washed with 30 ml of absolute ethanol. The solid was dried under vacuum (30 mmHg) at 40° C for 16 hours to give 8.2 g of moxifloxacin hydrochloride form A.

Please amend [0050] of the specification as follows:

[0050] 10 g of anhydrous moxifloxacin hydrochloride and 200 ml of ethanol with 0.3% K.F. were loaded into a 250 ml flask. The mixture was brought to reflux and kept in those conditions for 4 hours, after which it was cooled to room temperature. The solid product was filtered out and washed with 30 ml of absolute ethanol. The solid was recharged in a 250 ml flask, 200 ml of absolute ethanol with 0.1% K. F. were added and the mixture was brought to reflux and maintained in these conditions for 1 hour. Then

TURCHETTA et al
Appl. No. 10/580,173
January 26, 2009

the temperature was lowered to 25° ~~C~~ C and the crystalline solid was filtered and washed with absolute ethanol. After drying under vacuum (30 mmHg) at 40° ~~C~~ C for 16 hours 8.0 g of moxifloxacin hydrochloride form B were obtained.

Please amend [0051] of the specification as follows:

[0051] 20 g of moxifloxacin hydrochloride monohydrate and 250 ml of isopropanol with 0.2% K.F. were loaded into a 500 ml flask. The mixture was brought to reflux and was kept in those conditions for 4 hours, after which it was cooled to room temperature. The solid product was filtered and washed with 50 ml of isopropanol. The solid was recharged in a 250 ml flask, 200 ml of isopropanol with 0.1% K. F. were added and the mixture was brought to reflux and maintained in these conditions for 1 hour. Then the temperature was lowered to 25° ~~C~~ C and the crystalline solid was filtered and washed with isopropanol. After drying under vacuum (30 mmHg) at 40° ~~C~~ C for 16 hours 17.2 g of moxifloxacin hydrochloride form B were obtained.